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Advanced Maternal Age and the Risk of Down Syndrome Characterized by the Meiotic Stage of the Chromosomal Error: A Population-Based Study

by

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Summary

The identification of DNA polymorphisms makes it possible to classify trisomy 21 according to the parental origin and stage (meiosis I, meiosis II, or post-zygotic mitotic) of the chromosomal error. Studying the effect of parental age on these subgroups could shed light on parental exposures and their timing. From 1989 through 1993, 170 infants with trisomy 21 and 267 randomly selected control infants were ascertained in a population-based, case-control study in metropolitan Atlanta. Blood samples for genetic studies were obtained from case infants and their parents. Using logistic regression, we independently examined the association between maternal and paternal age and subgroups of trisomy 21 defined by parental origin and meiotic stage. The distribution of trisomy 21 by origin was 86 percent maternal (75 percent meiosis I and 25 percent meiosis II) 9 percent paternal (50 percent meiosis I and 50 percent meiosis II) and 5 percent mitotic. Compared with women less than 25 years of age, women 40 years old and older had an odds ratio of 5.2 (95 percent confidence interval, 1.0 to 27.4) for maternal meiosis I and 51.4 (95 percent confidence interval, 2.3 to 999.0) for maternal meiosis II. Birth prevalence rates for women 40 years old and older were 4.2/1000 births for meiosis I errors and 1.9/1000 births for meiosis II errors. These results support an association between advanced maternal age and both maternal meiosis I and II errors. The association with meiosis I does not pinpoint the timing of the error, however, the association with meiosis II implies that there is at least one maternal age-related mechanism acting around the time of conception.

Introduction

Down syndrome, one of the most common congenital anomalies, affects approximately one out of every thousand newborns (International Clearinghouse for Birth Defects Monitoring Systems 1991). It is the most intensively studied human chromosome abnormality, yet little is known about its cause, and only advanced maternal age has been confirmed as a risk factor (Janerich and Bracken 1986). Birth prevalence rates of Down syndrome plotted by maternal age form a J-shaped curve, with women from 20 through 24 years of age having the lowest prevalence rate (1/1400 births) (Hook and Lamson 1980; Erickson 1978). For women 35 years old, the rate is approximately 1/350 births and for women 45 years and older the rate rises to 1/25 births (Hook et al. 1983, Hook et al. 1988).

As much as 95 percent of Down syndrome is caused by trisomy 21, which typically results from nondisjunction during meiosis. Nondisjunction can occur during meiosis I (MI) when the chromosome pairs fail to separate or during meiosis II (MII) when the chromatids fail to separate. Studying the effect of maternal age on the meiotic origin of trisomy 21 could shed light on maternal exposures and their timing because MII errors occur around conception, whereas maternal MI errors could arise as early as during the mother's fetal life when meiosis is initiated.

Molecular techniques make it is possible to identify DNA polymorphisms on chromosome 21 and more accurately determine the parent and meiotic stage of origin of the extra chromosome. Earlier studies of parental origin relied on cytogenetic analyses, which are more subjective and more likely to result in misclassification. In 1984, Hassold and Jacobs summarized the results of the major cytogenetic studies and concluded that the extra chromosome was of maternal origin about 80 percent of the time and paternal origin 20 percent of the time. More recent studies using DNA polymorphisms to identify parental origin estimate the frequency of maternal and paternal nondisjunction at 90 to 95 percent and 5 to 10 percent, respectively (Sherman et al. 1991; Antonarakis and the Down Syndrome Collaborative Group 1991; Antonarakis et al. 1992). The analysis of chromosome 21 pericentromeric DNA polymorphisms has also made it possible to infer the meiotic stage of the chromosomal error. Evidence to date suggests that the majority of maternal nondisjunction is due to MI errors, whereas paternal nondisjunction is more often due to MII errors (Sherman et al. 1991; Antonarakis et al. 1992).

Recent studies of maternally derived trisomy 21 reported a higher mean maternal age for both MI and MII errors compared to controls (Sherman et al. 1994), and higher mean maternal age for MII errors compared to MI errors (Antonarakis et al. 1992). These studies were not population-based and included trisomy 21 cases from diverse sources, including therapeutic abortions, live births from different countries, and other convenient samples. Studies of trisomy 21 which are not population-based may be biased with respect to the parental origin of the extra chromosome and the age distribution of the parents. The studies were also limited in that they compared only mean parental ages and most did not adjust for spouse's age. Mean age does not account for differences in the age distribution of populations, nor does it describe the j-shaped nature of the risk curve for maternal age and trisomy 21. Adjusting for spouse's age is necessary in order to show the independent effects of maternal and paternal age. Our population-based, case-control study, which estimates the relative risk of maternally derived trisomy 21 due to advanced maternal age, addresses these limitations and is the first to combine an epidemiological analysis with molecular studies of the parent and meiotic/mitotic origin of nondisjunction.

Material and Methods

This investigation was part of a population-based, case-control study of trisomy 21 in the five-county area of metropolitan Atlanta. From 1989 through 1993, 170 infants with trisomy 21 were ascertained using the Metropolitan Atlanta Congenital Defects Program (MACDP), a birth defect surveillance system which uses active case ascertainment from multiple sources. Case finding and the criteria for inclusion in MACDP have been described in detail elsewhere (Lynberg and Edmonds 1992). From the same metropolitan Atlanta population, 267 unaffected control infants were randomly selected from hospitals in proportion to the expected number of total births at each hospital. Mothers and fathers of case and control infants were interviewed, and blood samples were obtained from the case infants and their parents in order to study the origin of the chromosomal error. During the 5-year study period (1989-1993), 192,597 infants were born to metropolitan Atlanta area residents. We obtained information on the ages of the infants' parents from vital records.

Laboratory Methods

Case infants and their parents were genotyped for markers located on chromosome 21. DNA was extracted from peripheral blood samples and/or lymphoblastoid cell lines, and Southern blotting techniques or the polymerase chain reaction were used to detect chromosome 21 polymorphisms. Twenty-nine markers were identified and grouped into 17 chromosome regions as described in Sherman et al. (1994). Each region was defined as a group of markers known to be tightly linked in normal individuals. Parental origin of the extra chromosome was determined by examining the contribution of alleles from each parent to their trisomy 21 offspring. Meiotic stage of origin was determined by comparing chromosome 21 pericentromeric markers of the parent who contributed the extra chromosome with those of the offspring. If parental heterozygosity was retained in the trisomic offspring (nonreduction) an MI error was concluded. If parental heterozygosity was reduced to homozygosity (reduction) an MII or mitotic error was concluded. MII and mitotic errors were distinguished by evaluating other non-pericentromeric loci. Those cases with markers that were reduced to homozygosity along the entire chromosome were considered mitotic errors, whereas the remaining were considered MII errors. Further details about the DNA analysis have been described elsewhere (Sherman et al. 1994).

Statistical Analysis

Based on the results of the DNA analysis, we grouped the cases according to the parental origin (maternal or paternal) and stage of origin (MI, MII, or mitotic) of the chromosomal error. We used logistic regression to study the effect of advanced maternal and paternal age on the risk of the MI and MII errors. The ages of the parents of case infants were compared with the ages of the parents of control infants and with the ages of the parents of all infants in the Atlanta population. This investigation, therefore, has two components: a case-control analysis and a case-population analysis.

For the analysis of maternally derived trisomy 21, we divided parental age into five groups (<25 years of age, 25-29 years of age, 30-34 years of age, 35-39 years of age, and $40 years of age) and the less than 25 year-old group was used as the referent category for estimating relative risk. Both maternal and paternal ages were included in the regression models to adjust for spouse's age. Results from the case-control analysis are presented as odds ratios with 95 percent confidence limits, and results from the case-population analysis are presented as rate ratios with 95 percent confidence limits.

Using the rate ratios from the case-population analysis, we estimated birth prevalence rates for the meiotic subgroups of maternally derived trisomy 21 by maternal and paternal age. The information required to estimate the birth prevalence rates were 1) the estimated population rate for the trisomy 21 subgroups, 2) the proportion of mothers and fathers in each age group for the birth population, and 3) the rate ratios (RR) for each parental age group. The population rates for maternally derived trisomy 21, maternal MI, and maternal MII were calculated by dividing the estimated number of cases of each subgroup (proportion of 170 cases ascertained as determined by results of the DNA analysis) by the total birth population. The proportion of mothers and fathers by age group was obtained from vital records and the rate ratios were obtained from the case-population analysis. For example, we used the following formula to calculate the age-group specific birth-prevalence rates for maternal meiosis I (MMI):

$$\frac{Estimated\ No.\ cases\ MMI}{Total\ \ births} = (proportion_{<25})(1)X + (proportion_{25-29})(RR_{25-29})X$$
$$+ (proportion_{30-34})(RR_{30-34})X + (proportion_{35-39})(RR_{35-39})X$$
$$+ (proportion_{\geq 40})(RR_{\geq 40})X$$

Where X = the absolute risk in the referent group.

The equation was solved for X, and X was multiplied by each rate ratio to obtain a birth prevalence rate for each age group. The rates are shown in Figure 1.

Results

Of the 170 infants with trisomy 21 ascertained for the study, 15 died or were adopted before they could be included in the study. The families of 130 of the remaining 155 infants (84 percent) agreed to participate in the study. The parental origin of the extra chromosome 21 could not be determined for 17 case infants; 8 infants required repeat blood samples and the loci studied for 9 case infants were uninformative. This meant 113 cases were informative with respect to parental origin. Of the 267 control infants identified, 179 (67 percent) agreed to participate in the study. Of the total birth population (192,597), 0.04 percent of the mothers' ages were missing from vital records, and 19 percent of the fathers' ages were missing.

Results of the DNA analysis revealed that 86 percent of the trisomy 21 cases were maternally derived, 9 percent were paternally derived, and 5 percent were due to mitotic nondisjunction. Of the maternally derived cases, 75 percent of the errors occurred during meiosis I, and 25 percent occurred during meiosis II. Eight of the maternally derived cases were uninformative with respect to meiotic stage of origin. Of the paternally derived cases, 50 percent were meiosis I errors, and 50 percent were meiosis II errors. Two of the paternally derived cases were uninformative with respect to meiotic stage.

Mean maternal and paternal ages were determined for the trisomy 21 subgroups (parent and meiotic stage of origin), the control infants, and the birth population (Table 1). Compared with the mean age of control mothers, the mean age of case mothers was significantly higher for all maternally derived cases (t test, $p < .001$), maternal MI cases ($p < .02$), and maternal MII cases ($p < .008$). The mean age of mothers for maternal MII cases was 2.5 years higher than the mean age of mothers for maternal MI cases but was not statistically significant ($p = 0.18$). Although the differences were not statistically significant, compared with the mean age of control fathers, the mean age of case fathers was lower for all paternally derived cases ($p = 0.76$), paternal MI cases ($p = 0.27$), and paternal MII cases ($p=0.60$). Mothers and fathers of the infants with mitotic errors had higher mean ages than the control parents but these differences were not statically significant.

For the analysis of maternally derived trisomy 21, relative risk was estimated for 5 groups of maternal and paternal ages using logistic regression. For comparison, the odds ratios from the case-control analysis are presented alongside the rate ratios from the case-population analysis (Table 2). Risk tended to increase with increasing maternal age for all maternally derived cases. This trend was also seen when the maternal MI and MII cases were considered separately. According to the case-control analysis, compared with women less than 25 years old, women aged 35 through 39 years old had a 3.7-fold increased risk for MI errors, and a 62.8-fold increased risk for MII errors. For women 40 years of age and older, the risk increased 5.2-fold for MI errors and remained high but slightly less for MII errors (OR = 51.4). The rate ratios for the case-population analysis show the same trends as the odds ratios from the case-control analysis, but the magnitude of the risks in the older age groups is slightly higher. From the odds ratios and rate ratios, it is evident that paternal age has no effect on the risk of maternally derived trisomy 21. We were not able to estimate risk of paternally derived trisomy 21 due to maternal and paternal age because there were too few cases.

Using the rate ratios from the case-population analysis we estimated the birth prevalence rates for all maternally derived trisomy 21, maternal MI, and maternal MII by maternal and paternal age groups (figure 1). The graphs show the rates per 1000 live births. As with the birth prevalence rates for all Down syndrome, the maternal age curves for both maternal MI and MII errors are nearly j-shaped, with a steep increase beginning at 35 years of age. The birth prevalence rate of maternal MI is 0.4/1000 births for women less than 25 years of age and rises to 1.2/1000 births for women 35 through 39 years of age and to 4.2/1000 births for women 40 years old and older. The birth prevalence rate of maternal MII is 0.03/1000 births for women less than 25 years of age and rises to 0.6/1000 births for women 35 through 39 years of age and to 1.9/1000 births for women 40 years old and older. The rates are greater for MI errors than for MII errors even though the estimated relative risks were higher for MII errors, reflecting the greater frequency of MI errors in the population. The birth prevalence rates of maternal meiosis I and II by paternal age (figure 1) show that paternal age has no effect on the population rates of maternally derived trisomy 21.

Discussion

Using a population-based, case-control study, we have determined the proportion of parental and meiotic subgroups of trisomy 21 and have estimated the effect of maternal and paternal age on the risk of maternally derived trisomy 21. In this population, nearly 90 percent of the trisomy 21 cases were maternally derived, and the majority of these cases resulted from meiosis I errors. Nine percent of the cases were paternally derived, with an equal number due to meiosis I and II errors. These results are consistent with those reported by others (Antonarakis et al. 1991; Sherman et al. 1991; Antonarakis et al. 1992), although ours is the first such study to be population-based.

The results of the logistic regression analysis showed that advanced maternal age was a risk factor for both maternal MI and MII errors. The estimated relative risks due to advanced maternal age were greater for MII errors than for MI errors, but the birth prevalence rates were greater for MI errors. Maternal MI errors were approximately 3 times more prevalent in the population than were MII errors. Although we did not study the parental age effect on the mitotic errors, research to date suggests that mitotic errors are not associated with advanced maternal age (Antonarakis et al. 1993).

Prior studies of trisomy 21 were limited by comparing only mean parental ages. Mean age does not account for differences in the age distribution of populations, nor does it describe the j-shaped nature of the risk curve for maternal age and trisomy 21. By estimating the relative risk for specific age intervals and adjusting for spouses' age we were able to estimate the independent effects of maternal and paternal age. One of the strengths of this population-based study was having two comparison groups— the randomly selected control group and the birth population for the five-county area of metropolitan Atlanta. Although the participation rate for the control group was only 67 percent, we were able to compare the age distribution of parents in the control group with the age distribution of parents in the birth population and were reassured that the distributions were similar. More importantly, we were able to reproduce our estimated relative risks in both the case-control and case-population analyses. Although the case-population analysis yielded higher relative risk estimates overall than did the case-control analysis, the trends were similar, and given the number of cases studied and the resulting 95% confidence limits, the estimates were within the same range, thus confirming our findings.

Another unique aspect of this study, because it was population-based, was the use of the rate ratios to estimate birth prevalence rates. Although the odds ratios derived from the case-control analysis are a good approximation of risk (because trisomy 21 is such a rare event), the birth prevalence rates derived from the population rates depict the actual prevalence of trisomy 21 for each parental age group on an absolute rather than a relative scale.

A limiting factor in this study was the impact of prenatal diagnosis. In this population, it has been estimated that at least 56 percent of women older than 35 years of age have prenatal testing done (Huether CA et al., University of Cincinnati, unpublished manuscript, 1992), and if the fetus is found to have trisomy 21, approximately 90 percent of the women choose to terminate the pregnancy (Drugan et al. 1990). The impact of this on our study is an underestimation of risk for advanced maternal ages and lower birth prevalence rates of trisomy 21 for women older than 35 years of age. In fact, our birth prevalence rates of trisomy 21 for women older than 35 years of age are about half the prevalence rates that were reported before prenatal diagnosis was common practice (Adams et al 1981). A recent study of the epidemiology of Down syndrome in metropolitan Atlanta found that terminations of pregnancies involving trisomic fetuses dramatically lowered the birth prevalence rates of Down syndrome enough to offset the increase in birth prevalence that would have resulted from higher average maternal age at birth (Krivchenia et al. 1993). If prenatal diagnoses were not a factor in this population, we would expect steeper birth prevalence curves beginning at 35 years of age.

The mechanisms by which advanced maternal age is associated with trisomy 21 are still unclear, but findings from this study provide further clues to the association between advanced maternal age and the timing of the meiotic errors. The association with meiosis I does not pinpoint the timing of the error, however, the association with meiosis II implies that there is at least one maternal age-related mechanism acting around the time of conception. To determine if advanced maternal age has a differential effect on meiosis I and II errors and to determine if there is a paternal age effect, more data are needed on the frequency of trisomy 21 among women 35 years and older, paternally derived trisomy 21, and the biological mechanisms that result in nondisjunction. Our study of trisomy 21 in metropolitan Atlanta is ongoing, and with the collection of more data, we will continue to study parental age effects as well as their associations with risk factors and other exposures both at conception and before.

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Table 1

Parental origin and meiotic stage of trisomy 21 cases and mean parental age of case infants, control infants, and birth population, Atlanta, Georgia, 1989-1993

Parental & Meiotic Origin	Frequency	Proportion	Mean Maternal Age ± S.D.	Mean Paternal Age ± S.D.
Maternal				
Meiosis I (MI)	67	MI/(MI+MII)=67/89=75.3%	29.5 ± 6.8	30.9 ± 6.1
Meiosis II (MII)	22	MII/(MI+MII)=22/89=24.7%	32.0 ± 7.3	34.1 ± 7.9
Meiosis error unkn	8		27.9 ± 5.9	27.7 ± 4.6

Subtotal	97	Mat/All=97/113=85.8%	29.9 ± 6.8	31.4 ± 6.6
Paternal				
Meiosis I (PI)	4	PI/(PI+PII)=4/8=50.0%	21.0 ± 5.5	24.8 ± 7.1
Meiosis II (PII)	4	PII/(PI+PII)=4/8=50.0%	25.0 ± 4.5	27.8 ± 6.2
Meiosis error unkn	2		29.0 ± 4.2	39.0 ± 5.7

Subtotal	10	Pat/All=10/113=8.8%	24.2 ± 5.4	28.8 ± 8.0
Mitotic errors	6	Mitotic/All=6/113=5.3%	29.5 ± 6.2	31.3 ± 5.6
Total Informative Cases	113		29.4 ± 6.9	31.2 ± 6.7
Controls	179		27.2 ± 6.0	29.6 ± 6.4
Atlanta population	192,597		26.9 ± 5.9	30.3 ± 6.4

S.D: standard deviation

Table 2

Estimated relative risk (adjusted for spouse's age) for maternally derived trisomy 21 associated with maternal and paternal age for the case-control analysis and the case-population analysis, Atlanta, Georgia, 1989-1993

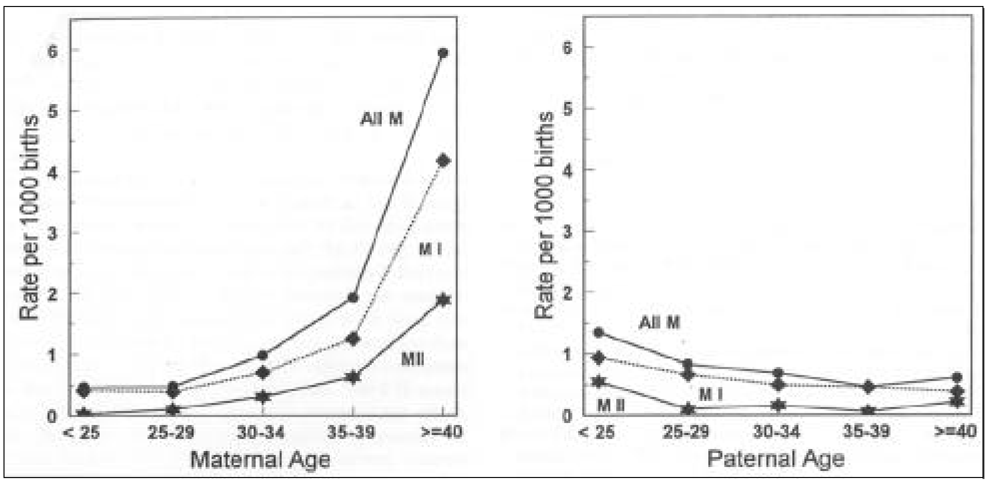
		Case-control analysis				Case-population analysis			
		Maternal Age		Paternal Age		Maternal Age		Paternal Age	
Trisomy 21 Subgroup	Age Groups	OR	95% CI	OR	95% CI	RR	95% CI	RR	95% CI
All Maternal	< 25	Ref.	--	Ref.	--	Ref.	--	Ref.	--
(N=92)[a]	25-29	1.29	(0.5-3.2)	0.58	(0.2-1.4)	1.02	(0.5-2.2)	0.61	(0.3-1.3)
	30-34	2.22	(0.8-6.1)	0.46	(0.2-1.3)	2.09	(0.9-4.7)	0.51	(0.2-1.2)
	35-39	5.29	(1.6-17.8)	0.28	(0.1-1.0)	4.11	(1.7-10.2)	0.34	(0.1-0.9)
	$ 40	6.54	(1.4-29.5)	0.59	(0.2-2.3)	12.68	(4.3-37.8)	0.45	(0.2-1.2)
Maternal Meiosis I	< 25	Ref.	--	Ref.	--	Ref.	--	Ref.	--
(N=66)[a]	25-29	1.20	(0.5-3.2)	0.69	(0.3-1.8)	0.95	(0.4-2.2)	0.71	(0.3-1.7)
	30-34	1.80	(0.6-5.4)	0.50	(0.2-1.6)	1.73	(0.7-4.4)	0.52	(0.2-1.4)
	35-39	3.70	(1.0-14.0)	0.42	(0.1-1.6)	3.06	(1.1-8.9)	0.48	(0.2-1.5)
	$ 40	5.19	(1.0-27.4)	0.56	(0.1-2.5)	10.21	(2.8-37.7)	0.40	(0.1-1.4)
Maternal Meiosis II	< 25	Ref.	--	Ref.	--	Ref.	--	Ref.	--
(N=20)[a]	25-29	5.14	(0.5-50.6)	0.10	(0.0-1.2)	3.46	(0.4-28.5)	0.18	(0.0-1.4)
	30-34	16.42	(1.1-240.5)	0.18	(0.0-1.9)	10.56	(1.2-91.4)	0.28	(0.0-1.7)
	35-39	62.81	(3.4-999.4)	0.04	(0.0-0.6)	21.63	(2.2-213.2)	0.09	(0.0-0.8)
	$ 40	51.42	(2.3-999.0)	0.29	(0.0-4.1)	64.83	(5.5-764.8)	0.38	(0.1-2.8)

OR = odds ratio; RR = rate ratio; CI = confidence internal; Ref. = reference group

[a] Number of cases included in regression models is less than totals from Table 1 because of missing paternal ages.

Figure 1

Estimated birth prevalence rates (adjusted for spouse's age) of maternally derived -trisomy 21 by maternal and paternal age, Atlanta, Georgia, 1989-1993



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